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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/120,030	07/21/1998	BETH P GOLDSTEIN	70021.0022USU1	1743

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EXAMINER	
BORIN, MICHAEL L	

ART UNIT	PAPER NUMBER
1631	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/120,030	GOLDSTEIN ET AL.	
	Examiner	Art Unit	
	Michael Borin	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 March 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *67-84,86-89 and 92-94* is/are pending in the application.

4a) Of the above claim(s) *67-78* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *79-84,86-89,92-94* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 03/01/2010 has been entered.

Status of the claims

1. There are no amendments to the claims. Claims 67-84,86-89,92-94 are pending. Claims 67-78 remain withdrawn from consideration.

Applicant's arguments have been fully considered but were not deemed persuasive . The following rejections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 82, 94 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Claims 82,94 introduce new matter in claiming dosage of 15 mg/kg/day administered to humans. Note, that Table 6 in specification described administration of lysostaphin to rabbits, not to humans as claimed.

Response to arguments

Applicant asserts that examples provided for administration to rabbits provide sufficient support for the dosage to be administered to humans, because rabbit model is an accepted animal model. Examiner does not dispute that the rabbit model is an accepted animal model. However, the dosages in rabbits do not necessarily translated into the same dosages in humans.

Claim Rejections - 35 USC § 103.

3. Claims 79-84,86-89,92-94 are rejected under 35 U.S.C. 103(a) as unpatentable over Zygmunt, and Goldberg and Stark, and further in view of Oldham. The rejection is maintained for the reasons set forth for claims 79-89,92,93 in the previous Office action.

The instant claims are drawn to method of treating staphylococcal infection in a human subject comprising administration of a recombinantly produced lysostaphini in a dose from 5 to 20 mg/kg/day.

Zygmunt

Zygmunt et al is a general reference reviewing properties of lysostaphin, its *in vitro* and *in vivo* applications, and various ways of administration. The reference teaches that lysostaphin is effective against a wide variety of staphylococcal infection, and is more potent than penicillins. The reference describes treatment of staphylococcal infections in various organs, such as kidney, heart valve (pages 319-325). The ways of administration are both systemic and topical (pages 319-324). The dosages of lysostaphin vary depending on the ways of administration; thus reference cites use of single doses in the range of 0.5 to 50 mg/kg (p. 320, Table 4), or multiple doses in the range of 0.5 to 50 (p.523, bottom addressing study of Goldberg et al; see discussion of Goldberg reference below). Thus, both the dosage and ways of administration are

result-effective variables which may be optimized by an artisan in a course of routine optimization. Combined therapy with other antimicrobials, such as methicillin, augments effect of lysostaphin (p. 322). The reference also teaches pharmaceutical compositions comprising lysostaphin.

Zygmunt reviews a number of studies of the efficacy of lysostaphin in treating established staphylococcal infections in animals, including Goldberg's study, discussed below (Zygmunt 318-324).

In another reviewed study, 100% of mice infected with an otherwise lethal intraperitoneal staphylococcal infection survived when treated with a single intravenous dose of lysostaphin, in contrast to 53% survival in mice treated with penicillin G instead (Zygmunt 319).

In yet another reviewed study, mice with established methicillin-resistant staphylococcal renal abscesses demonstrated the effectiveness of a single dose of lysostaphin followed by daily doses of methycillin on succeeding days, "suggest[ing] that a single exposure to lysostaphin may increase the susceptibility of staphylococci to eventual destruction by methicillin" (Zygmunt 322-323).

There are potential risks associated with using lysostaphin to treat established staphylococcal infections in humans, that must be balanced against the potential benefits, as with antimicrobial therapy in general (Zygmunt 326-327, and 330-331).

For example, while Zygmunt cautions that "[o]ne should view lysostaphin as a potentially sensitizing protein when administered systemically to man" (Zygmunt 330), he also notes that "no evidence has accumulated thus far that lysostaphin is sensitizing

to man" (id. at 331), and suggests that "[a] limited course of therapy.., may involve only marginal risk" (id. at 330). Zygmunt further notes that "[a]lthough in vitro resistance to lysostaphin can be observed frequently in the laboratory [ ], this phenomenon has not been a problem in the in vivo situation" (id. at 325), and "no strains of staphylococci naturally resistant to lysostaphin have been detected in more than 1,000 human clinical isolates of [ ] staphylococci tested" (id.).

While Zygmunt concludes that "the potential for [sensitization to lysostaphin].., seems too high to risk in an era when staphylococcal disease appears to be generally well controlled by existing antibiotics" (id. at 331), he acknowledges that others of skill in the art "take[ ] the position that lysostaphin should be evaluated systemically in man for severe staphylococcal infections[,]" particularly in light of "the increasing number of reports that have appeared in recent years on the occurrence of methicillin-resistant staphylococci" (Zygmunt 330).

In addition, Zygmunt suggests that "lysostaphin could provide a reserve mode of therapy in dire situations" (Zygmunt 330), "[s]ince none of the clinically available antibiotics is able to lyse large numbers of staphylococci regardless of their metabolic state with the effectiveness of lysostaphin" (id.), and further suggests that lysostaphin "be tested in those instances of human staphylococcal disease where it is imperative to decrease the number of microorganisms present in infected tissues (endocarditis, infected vascular grafts, atrioventricular shunts, etc.)" (id.).

Zygmunt also suggests that it could be beneficial to administer lysostaphin in combination with a semisynthetic penicillin (Zygmunt 330). The underlying rationale is

that "initial lysostaphin therapy may lower the titers of staphylococci within established lesions sufficiently to allow conventional antimicrobials to exert a therapeutic effect and to enable the host's defense mechanisms to function more effectively. In addition, the rapid elimination of circulating staphylococci in cases of staphylococcal bacteriemia may prevent metastatic infection" (id. at 330-331).

With respect to dosage levels in humans, Zygmunt suggests that "short-term intravenous doses to man in the range of 10 mg/kg b.i.d. [i.e., twice a day] of lysostaphin might be expected to cause no serious toxic effects" (Zygmunt 327).

Goldberg

Goldberg et al teach treatment of staphylococcal infection in dogs with lysostaphin used intravenously at dosages 5-50 mg/kg. The administration was done multiple times, at intervals 1 to 24h. Treatment courses consisted of 1 to 23 injections over periods of 5h to 6.5 days. When recalculated to the amounts in mg/kg/day, i.e., as used in the instant claims, dogs 4, 5, 7, and 10 received 35.4, 31.6, 17.6, and 13 mg/kg/day, respectively [1]. Although lysostaphin administration was followed in relapse in some dogs (dogs 7 and 10), administration of lysostaphin caused from substantial reduction to complete clearance of infection. See Table 1. Lysostaphin treatment was effective in treatment of infection in lung, liver, spleen, kidney, and aortic and mitral valves. Heart valves were the most easily sterilized tissue. Adverse reactions to lysostaphin were not observed. See abstract and Table 1.

Note, that the amount of lysostaphin which resulted in successful treatment of dogs (no relapse) of dogs 4 and 5 (Table 4), is only marginally different from the claimed amount of up to 30 mg/kg/day of recombinantly produced lysostaphin for treatment of humans as claimed in claims 4,5, or up to 25 mg/kg/day as claimed in claims 45-47. See further discussion in the Response to Arguments below

. Goldberg describes a study wherein thirteen dogs infected with experimental acute staphylococcal endocarditis were treated with lysostaphin "administered intravenously in doses of 5 to 50 mg/kg at intervals of 1 to 24 hr. Treatment courses consisted of 1 to 23 injections over periods of 5 hr to 6.5 days" (Goldberg Abstract).

All thirteen dogs in Goldberg's study improved clinically after initial therapy. Three experiments were terminated while the dogs were improving, five dogs became clinically well, and five relapsed (Goldberg Abstract). "One relapsed dog [ ] received only a single 50 mg/kg dose, and three other relapsed dogs [ ] received the smallest individual doses in the series of 13 dogs" (id. at 48, col. 1). The fifth dog that relapsed did so after a surgical accident (id.).

"Regardless of the size of the dose, [lysostaphin] therapy resulted in a [substantial] decrease in the number of staphylococci circulating in the blood" and "[q]uantitative culture of tissues showed that lysostaphin treatment resulted in decreased numbers of staphylococci in lung, liver, spleen, kidney, and aortic and mitral valves[;] [h]eart valves were the most easily sterilized tissue" (Goldberg Abstract).

"Adverse reactions to lysostaphin were not observed" (Goldberg Abstract).

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1 All amounts hereinafter are recalculated into mg/kg/day as (Mean dose)x(No. doses)/(No days

"[L]ysostaphin's selective action against S. aureus and no other bacteria would permit its use without the fear of super-infection common to most antibiotics which alter the bacterial flora of man" (Goldberg 51, col. 2). Another advantage of lysostaphin over other antibiotics is its "rapid killing at any stage of growth" (Goldberg 51, col. 2).

Zygmunt and Goldberg references do not teach administration of lysostaphin to humans.

Stark

Stark et al describes systemic administration of lysostaphin to a man suffering from staphylococcal pneumonia resulting from terminal unresponsive leukemia. The reference demonstrates that parenteral systemic administration of lysostaphin reduces bacteremia caused by strain of S. *Aureus* which proved to be resistant to methicillin, vancomycin and cephalothin. Single treatment with lysostaphin resulted in a complete clearance of microorganisms from pustule sites. The treatment also removed staphylococci from blood, lungs, or abscess site.

Stark teaches that lysostaphin effectively cleared methicillin-resistant Staph. aureus (MRSA) from infected abscesses in a neutropenic patient (Stark 240).

"Despite potential immunogenicity, controlled trials of lysostaphin may be indicated now as adjunctive therapy in human staphylococcal infections in which

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treated) as suggested by applicant in response filed 10/20/2003

mortality and morbidity remain high, as in overwhelming or resistant involvement of lung, liver, brain, endocardium, and bone by Staph. aureus" (Stark 240).

The references above do not teach recombinant lysostaphin or use thereof. It is well established in the art that recombinant way of production of proteins is easier and more effective than non-recombinant methods (such as organic synthesis or purification). Oldham reference is used to demonstrate that lysostaphin can be produced recombinantly and that the product produced thereby has high antimicrobial activity similar to that of the natural product.

Oldham

Oldham et al teaches that lysostaphin can be produced recombinantly and demonstrates that recombinant lysostaphin, at low concentration of 5 µg/ml, is effective against *S. Aureus* in mammary tissue. See abstract. Note that administration to mammary tissue reads on the instantly claimed systemic administration, as the latter encompasses direct delivery to organs through injection (see specification, page 6, lines 31-32)

The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior

art; and (4) secondary considerations of nonobviousness, if any. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 148 USPQ 459,467 (1966). "When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that is was obvious under § 103." *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1742 (2007).

The references of record establish that one of skill in this art would have recognized, and been accustomed to weighing, the relative risks and benefits of antimicrobial therapy (as demonstrated in Zygmund). That being the case, administering lysostaphin to humans to treat established staphylococcal infections would have been obvious to one of skill in the art at the time of the invention (and indeed was explicitly suggested by persons of skill in the art (as addressed in Zygmund, p. 330,331 cited above), despite lysostaphin's potential for immunogenicity, given the recognition in the art that staphylococcal infections resistant to conventional antibiotics (e.g., methicillin-resistant *Staph. aureus* (MRSA) infections) are often sensitive to lysostaphin, the recognition that it is imperative to rapidly decrease the sheer number of microorganisms present in infected tissues like heart valves and in infections associated with devices like atrioventricular shunts, the recognition that "none of the clinically available antibiotics is able to lyse large numbers of staphylococci regardless of their metabolic state with the effectiveness of lysostaphin" (Zygmund, p. 330, cited above), and the

recognition that lysostaphin is highly selective and can be used without fear of super-infection common to most antibiotics which affect the bacterial flora of humans less-selectively (Goldberg, p. 51, col. 2, cited above).

Further, a short-term intravenous administration of lysostaphin in the range of 10 mg/kg, twice a day - a protocol that meets the requirement of the claims - would have been obvious, given Zygmunt's suggestion that this particular protocol would not be expected to cause adverse reactions in humans (Zygmund, p. 327, cited above).

Further, it would have been obvious for one of skill in the art to administer recombinant lysostaphin,rather than native lysostaphin, given the availability of the recombinant product and its comparability to native lysostaphin (as demonstrated by Oldham).

The invention of claims 32, 46, 47, 50, 51, 56, 58, and 59 would have been obvious over the teachings of Zygmunt, Goldberg, Stark, Oldham, and Dixon. It would have been obvious for one of skill in the art to have administered lysostaphin in combination with another antimicrobial agent, given the recognition that lysostaphin acts quickly to kill most, but not necessarily all, of the Staphylococci present in an established lesion, while at the same time, rendering the remaining organisms more susceptible to other, conventional antimicrobials

Therefore, the prior art teaches that lysostaphin is effective both *in vitro*, in animal studies, and in humans. In regard to multiple administration to humans, as Goldberg teaches that lysostaphin is effective in animal studies when taken either in a

single dose or repetitively, it would be obvious to select an appropriate regime of administration in humans as well. In regard to the particular dosage ranges, first, Goldberg teaches dosage range that overlaps with the claimed dosage ranges. Second, if there are any differences between dosage ranges as claimed and that of the prior art, the differences would be appear minor in nature; in addition as the dosage is an result-effective variable, as can be clearly seen from, e.g., Goldberg, selection of the dosage, protocol and route of administration will be obvious to one skilled in the art as a result of routine optimization.

With respect to claims 80,81,92,94, in regard to various locations of treatment, as Zygmunt teaches that lysostaphin is effective against more than 300 staphylococcus species and suggests its wide use at various locations, and as Stark suggests use of lysostaphin for treatment of human staphylococcal infections in lung, liver, brain, endocardium, and bone, it would have been obvious to an artisan to apply this versatile antimicrobial at the sites which require antimicrobial treatment with the expectation, in the absence of evidence to the contrary, that such treatment will be successful.

The Board of Appeals and Interferences, considering the previously present claims of the instant application, provided the following considerations:

> We have considered Appellants arguments and the Declaration of Dr. Michael Climo, but are not persuaded otherwise, for the reasons discussed below.
>
> Appellants argue that "Goldberg... teaches that dosages in the claimed range do not achieve the same result as [ ] higher dosages but, rather, result in an unacceptable increase in resistant strains and eventual relapse of the dogs being treated" (Appeal Br. 5 ~0), and "dosages of up to 25 mg/kg/day.., are substantially lower than any dosage

administered to a 'well' or 'improved' dog in Goldberg" (id. at 9). Appellants also rely on Dr. Climo's assertion that "treatment of experimental canine endocarditis... 8 The Answer referred to here and elsewhere in this opinion is the Supplemental Examiner's Answer mailed October 30, 2006. The Declaration of co-inventor Michael Climo, M.D. (hereinafter "Decl."), dated September 27, 2001, submitted under 37 C.F.R. § 1.132, and resubmitted with the Appeal Brief.

The Appeal Brief referred to here and elsewhere in this opinion is the Third Replacement Appeal Brief filed February 2, 2006. cannot be extrapolated to treatment of humans. Nor is it predictive of the efficacy of treatment in humans" (Decl. ¶9).

In a similar vein, Appellants argue that Stark's study "involved a single human and is more speculative of treatment in humans than conclusive" (Appeal Br. 7), and does not "teach[ ] or suggest[ ] that lysostaphin is effective as routine bactericide treatment in humans for systemic infection" (Decl. ¶ 10). Appellants also argue that Oldham "is limited to the treatment of a specific staphylococcal infection not found in humans, namely bovine mastitis" (Appeal Br. 8), and "[o]ne of skill in the art would recognize that non-systemic use of recombinant lysostaphin in a non-human model is not predictive of systemic use in humans" (Decl. ¶ 12).

These arguments are not persuasive, particularly as none of the arguments addresses Zygmunt's or Stark's teachings and suggestions regarding the use of lysostaphin in treating staphylococcal infection in humans. The claims are directed to systemic administration of lysostaphin to treat established staphylococcal infections in humans, and the prior art establishes that administration of lysostaphin to humans was specifically contemplated in instances of "established," "overwhelming," or "resistant" staphylococcal infections in humans prior to Appellants' invention (FF 13, 17). Moreover, the claims require administration of lysostaphin in an amount ranging from 0.5 to 30 mg/kg/day, or in an amount up to 25 mg/kg/day. Zygmunt explicitly suggests administering lysostaphin intravenously at a dose encompassed by the claims: 10 mg/kg, twice a day, i.e., 20 mg/kg/day (FF 15).

Finally, with respect to the use of recombinant lysostaphin, Dr. Climo notes that Oldham teaches that "recombinant lysostaphin 'is highly immunogenic when administered to some species parenterally in adjuvant'" (Decl. ¶ 13), and argues that "[o]ne of ordinary skill in the art would instantly recognize, therefore, that such a highly immunogenic protein is eminently unsuitable for systemic use" (id.).

This argument is not persuasive. The fact that a protein might be immunogenic when administered with an adjuvant does not necessarily mean that it will be immunogenic when administered without an adjuvant, as would be the case in a treatment protocol. At any rate, as discussed above, Zygmunt notes that "no evidence has accumulated thus far that lysostaphin is sensitizing to man" (Zygmunt 331), and suggests that "[a] limited course of therapy.., may involve only marginal risk" (id. at 330) (FF 11).

Response to arguments

Applicant's arguments have been considered but were not deemed persuasive, and have been already addressed on multiple occasions in the preceding Office actions and/or in the Board decision. The rejection is maintained.

This is a RCE of applicant's earlier Application No. 09/120030. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Borin whose telephone number is (571) 272-0713. The examiner can normally be reached on 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie Moran can be reached on (571) 272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael Borin/
Primary Examiner, Art Unit 1631